NTP
National Toxicology Program

CERHR Update and Evaluation Concept:

State-of-the-Science Evaluation on Environmental Exposures and Diabetes/Obesity

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Outline

- New CERHR staff
- Updated evaluation of soy formula
- Concept proposal for state of the science assessment of environmental contaminants and diabetes/obesity

New CERHR Staff

- 4 new staff since August 2009
  - Vickie Walker, BS
  - Kyla Taylor, MS
  - Andy Rooney, Ph.D
  - Kembra Howdeshell, Ph.D
- Total staff of 6
  - 4 new staff, Mike Shelby, Kris Thayer

Soy Formula Evaluation

- **October 19, 2009:** Release draft Expert Panel Report
- **December 16 – 18, 2009:** Expert Panel meeting
- **Early January 2010:** Release final Expert Panel report for public comment
- **March 2010:** Release Draft NTP Brief on Soy Formula for public comment
- **May 10, 2010:** Peer review of draft NTP Brief by BSC
- **Summer 2010:** Release final NTP Monograph on Soy Formula

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Concept Proposal

State-of-the-science evaluation of environmental exposures and diabetes/obesity

Justification

- Diabetes and obesity are major threats to human health
  - ~40% of people ≥20 of age have diabetes or pre-diabetes, NHANES 2005-2006 (Cowie 2009)
    - 12.9% diabetes (of which ~40% undiagnosed); 29.5% with pre-diabetes (impaired fasting glucose or impaired 2-hour glucose tolerance)
  - ~70% of type 2 diabetes risk attributed to overweight/obesity (Eyre 2004),
    - Thus, ~30% not accounted for by body weight
  - Often discussed in the context of developmental origins of adult disease or prenatal programming, e.g., PPTOXII, Miami December 7-10, 2009
  - Risk factors for impaired reproduction/development

Justification

- Growing scientific and public interest
  - Organohalogens: ~ 40 human studies since 2005 (~70 total)
  - Arsenic: Odds ratio of 3.58 (95%CI: 1.18-10.83) for type 2 diabetes based on comparison of 80th and 20th percentiles of total urinary arsenic, 2003-2004 NHANES data (Navas-Acien 2008)
  - BPA: Higher urinary levels associated with diabetes and cardiovascular disease, 2003-2004 NHANES data (Lang 2008)
    - Diabetes: Odds ratio per 1-SD increase in BPA concentration = 1.39 (95% CI: 1.21-1.60)
  - Newsweek, September 11, 2009 "Born to be Big: Early Exposure to Common Chemicals may be Programming Kids to be Fat"

Goals and Expected Outcomes

Charge 1: Critical assessment of the current literature

a) Evaluate strength/weaknesses, consistency, and biological plausibility of findings reported in humans and experimental animals within and across chemicals;
   - NOT intended to develop "level of concern" conclusions

b) Identify the most useful and relevant endpoints in experimental animals and *in vitro* models

Charge 2: Focus future research directions

a) Identify data gaps and areas for future evaluation/research

Proposed Approach - Workshop

Present concept to NTP Board of Scientific Counselors

CERHR staff prepare literature review document

Identify experts and convene subpanels of scientists to address charge #1 (critical assessment of current literature) for each exposure chapter

Public Comment

Public Workshop (early Fall 2010)

Oral public comments

Subpanels finalize responses to charge #1, present in plenary

- Group discussion on subpanel findings`

Second round of subpanels meet to address charge #2 (data gaps and research needs)

- Group discussion on research needs

Open general discussion

Prepare NTP Monograph (late Fall 2010)

Workshop report as executive summary + literature review document
(workshop report also submitted for publication)

Literature Screen

- Use of a combination of health- and exposure-based MeSH terms
- Iterative process
  - Wish list: broad screen of environmental exposures for effects related to diabetes, metabolic syndrome, and obesity
  - A front end screen for health-effects related to metabolic syndrome not feasible, i.e., too many articles retrieved
    - Can be follow-up search for specific exposures
  - "Obesity" not a precise MeSH heading for this evaluation
    - Targeted approach
  - MeSH terms for environmental exposures too broad*
    - Focus on specific exposures or classes of chemicals

*MeSH headings: environmental pollution, toxic action, endocrine disruptors

Extent of Literature

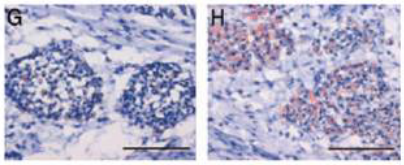
- Nature of literature varies from exposure to exposure, i.e., number of publications, proportion of human/animal/in vitro
  - Relatively large literatures
    - Arsenic, organochlorines (e.g., dioxin, PCBs, DDT/DDE), genistein
  - Relatively small literature
    - Organotins, BPA, phthalates
- Thus, the type of conclusions reached for each type of exposure will vary
  - Range from research focusing to those that permit drawing conclusions on consistency/biological plausibility

Approach to Assess "Obesogens"

- Targeted search
  - e.g., tributyltin, genistein, BPA, DEHP, PFOA
  - Consider consistency of effects on body weight following developmental exposure
  - BUT, recognize that topic is more complex than effects on body weight

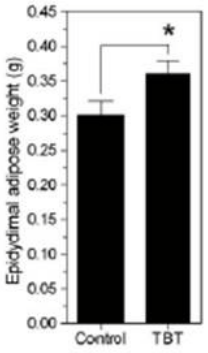
Tributyltin as Inducer of Adipogenesis (Grun et al., 2006)

- C57BL/6 dams treated with 0.5 mg/kg TBT by ip injection on GD12-18; looked at effects in F1 offspring:
  - ↑ lipid accumulation in adipose depots, liver and testis in neonates
  - ↑ epididymal adipose mass in adult male offspring
  - No effects on body weight in adult mice

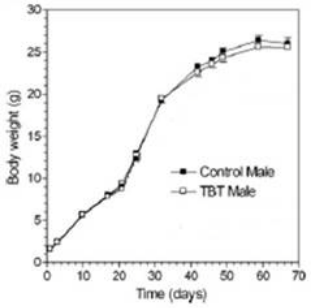


Control TBT

Mammary adipose tissue in neonates
(Oil red O stain)



F1 males at 10 weeks



Type of Scientific Expertise

- **Charge 1: Critical assessment of the current literature**
  - Include expertise in particular exposures as well as expertise in the primary health conditions
- **Charge 2: Focus future research directions**
  - Overlap with 1st subpanel membership, but supplemented with others to generate both general research suggestions as well as those specific to NIEHS/NTP

Charge to Board

To review and comment on proposed CERHR evaluation concept and determine whether the evaluation is an appropriate use of NTP program resources.

- Rationale
- Merit
- Overall significance and public health impact
- Scope of review activity
- Other comments

References

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Lang *et al.*, 2008. Association of urinary bisphenol A concentration with medical disorders and laboratory abnormalities in adults. Jama. 300:1303-1310.

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Ohlsson *et al.*, 2000. Obesity and disturbed lipoprotein profile in estrogen receptor-alpha-deficient male mice. Biochem Biophys Res Commun. 278(3):640-5.